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Disease-a-Month

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Allergic Dermatitis

RICHARD B. STOUGHTON

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Allergic Dermatitis

RICHARD B. STOUGHTON

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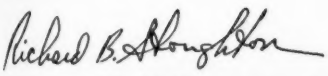

received his M.D. degree from the University of Chicago School of Medicine. After taking his residency training at this institution, he was appointed Instructor in Dermatology in 1951 and is at present Assistant Professor of Dermatology at the University of Chicago. He carries on a full-time program of teaching, clinical work, and research. His principal interests in research are connective tissue components of skin and mechanisms of blister formation. He has written numerous articles concerned with clinical and research problems in dermatology.

THE SKIN, like any other organ, may be the battleground of antigen and antibody. It differs from other organs in that it is far more commonly such a battleground. Poison ivy dermatitis alone probably occurs in more people than any other allergic disease, including hay fever. Rare is the practicing physician who hasn't seen at least a few examples of penicillin urticaria, barbiturate-induced eruptions, or many other drug-induced skin eruptions, and common must be the physician who sees such cutaneous sensitizations almost every day.

Contact dermatitis and dermatitis medicamentosa are by far the most prevalent types of allergic dermatitis, and there is little argument that an allergic mechanism is responsible for these diseases. Acute urticaria is almost always of allergic nature whether it be from lobster, strawberries, other foods, or medicaments. Chronic urticaria may have an allergic basis, but a causative allergen is rarely found. Many authorities include atopic eczema or neurodermatitis as an allergic skin disease, but others do not. Whatever the truth is, there are many characteristics of atopic dermatitis or neurodermatitis which suggest an allergic basis but practically never is a specific allergen found which can be shown to be responsible for the disease. Because of the controversial nature of the etiology of atopic dermatitis, less space will be given to its discussion than to other perhaps less common and less severe conditions of known allergic etiology.

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'Id' reactions in which a site distant from a focus of infection (bacterial, viral, fungal) reacts to a circulating antigen will be taken up in more detail.

Though somewhat rare, physical allergies such as urticarial reactions to heat, cold, ultraviolet light and slight trauma will be discussed because they are unique in that the antigen is, at least originally, a physical rather than a chemical entity. Finally, there may be many dermatoses of unknown etiology which may eventually be proved to have an allergic basis. In fact there is hardly a dermatitis of unknown etiology which has not at some time or other been suspect for an allergic basis.

One is always fearful of the lax use of the term "allergic." Some serious workers in the field have suggested the word be buried. It is well to keep in mind the caution of Sulzberger (1)—that if you are going to say "allergic," you must always ask "allergic to what?"

MORPHOLOGIC TYPES OF ALLERGIC REACTION IN SKIN

The protean morphologic appearance of skin lesions of allergic nature seems at first a bit bewildering. Differences in severity of response, or different localization of the reaction within the skin, may well account for the variety of lesions one may see. Also a number of different chemicals may be liberated by the antigen-antibody reaction. For instance, histamine, which gives the typical urticarial wheal (2), is liberated in some cases of antigen-antibody union and not in others.

Common to practically all allergic reactions in the skin is involvement of vessels which may result in fluid leakage (edema), vasodilation (erythema), loss of red cells (hemorrhage), or outpouring of white cells (infiltration). Vessels of the superficial plexus may be primarily involved, giving rise to flat morbilliform and scarlatiniform reactions; or the deeper cutaneous and subcutaneous vessels may react, giving lesions of erythema nodosum.

Severe edema with urticarial reactions and erythema multiforme may result in vesiculation and blistering. Vesicles and blisters also occur commonly, indeed are characteristic, in reactions primarily involving the epidermis, as in contact dermatitis.

Table 1 gives the morphologic types of allergic dermatitis and some common etiologic agents for each type.

TABLE 1.—Morphologic Types of Reaction

Morphologic Type	Common Example of Etiologic Agent
Urticarial wheal	Penicillin, horse serum, foods
Vesicles and bullae	Poison ivy, chromates, fungus
Scarlatiniform and morbilliform	Barbiturates, sulfa drugs
Hemorrhagic (purpura)	Barbiturates, arsenicals, mercurials
Acneform	Bromides, iodides
Infiltrated (erythema nodosum)	Sulfa drugs, tuberculosis, coccidioidomycosis
Papular	Positive tuberculin and histoplasmin skin tests
Eczematous (edema, vesicles)	Poison ivy, chromates, etc.

Allergic cutaneous reaction types are often classified according to whether they are immediate (1–30 minutes) or delayed (24–48 hours) after the introduction of antigen into a sensitized area. The immediate type is urticarial and the delayed type is either primarily epidermal (eczematous) or dermal (tuberculoid). The late, delayed reaction of the Kveim skin test (sarcoidosis) fits neither of these groups. It is of interest that the immediate type is histaminic in nature and responds to antihistamines, whereas the delayed types have nothing to do with histamine and do not respond in the least to antihistaminic drugs.

ANTIGEN AND ANTIBODY IN CUTANEOUS ALLERGY

Circulating antibodies are usually quite easily demonstrated in the serum of people with allergic urticarial reactions. The easiest and most convincing way of demonstrating circulating antibody is the Prausnitz-Küstner test. In this test, serum from the allergic patient (e.g., one who is allergic to fish) is injected into the skin of a normal (non-allergic) subject. The normal subject then ingests fish or the fish antigen may be applied directly to the previously sensitized area. An urticarial reaction will develop at the site of the serum injection either with oral or direct exposure to fish protein. A positive response with adequate negative controls demonstrates circulating antibodies.

People with neurodermatitis, hay fever, and asthma as well as urticaria frequently carry these circulating antibodies, as do many members of the family. These people are known as atopic types and the characteristic skin disease they manifest is frequently called atopic eczema. What role this atopy actually plays in their skin disease is at best a matter of speculation.

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Peculiarly, people with urticarial response to penicillin and other drugs rarely carry demonstrable circulating antibodies.

In contact dermatitis circulating antibodies have never been adequately demonstrated by the passive transfer method (3). In fact, antibodies of any kind are extremely difficult to show in contact dermatitis, whatever the offending agent may be. Haxthausen (4) demonstrated the transfer of sensitization from one guinea pig to another if the circulations were interconnected (parabiosis) during the sensitization of one of the animals. He has also shown that in uniovular twins a skin graft from one twin sensitized to a compound will retain this sensitization when grafted on the non-sensitized twin (5). This sensitization reaction in the graft disappears in time, however, indicating that sessile antibodies are present within the skin cells. Also the non-sensitized graft became sensitive a short time after being grafted to the previously sensitized twin. Practically all attempts to transfer the contact type of sensitization by the Prausnitz-Küstner method have ended in failure. We must conclude that there are no significant levels of circulating antibodies in individuals with contact eczematous types of sensitization and that the antibody is probably fixed in the skin. The origin of antibodies in eczematous dermatitis is believed to be distant to the skin (3). If the deep lymphatics are cut widely under a small area where the potential sensitizing agent is applied, no sensitization will occur. The antigen presumably stimulates antibody formation at a site distant to the skin. Thus there must be, at some time, circulating antibodies in order to return them to the skin from their site of origin. It is possible that the antibody concentration is too low to detect or that the antibodies are transported in an inactive form.

Intradermal placement of a suspected antigen by scratch or injection methods may elicit an immediate type of urticarial reaction if antibodies are present. These antibodies may be of a circulating or sessile type but circulating antibodies are usually present. If the antigen creates a delayed response (such as the tuberculin and histoplasmin reactions) *circulating* antibodies cannot be demonstrated.

The antigen in urticarial reactions is usually a complicated molecule and frequently a protein. In contrast, the antigen in eczematous sensitization is usually a simple compound and some-

times a simple inorganic ion such as nickel, chromium, gold, or arsenic. The original work of Landsteiner and Chase (6) showed quite clearly that simple compounds combine with protein to give the actual antigen. This is probably what takes place in clinical sensitization of the eczematous type.

Some simple compounds are extremely common sensitizers and are used as antigens in experimental studies. Examples of these are paraphenylenediamine, poison ivy extract, dinitrochlorobenzene, and picryl chloride. Close chemical relatives of known antigens may also act as antigens so that a whole family of compounds and even seemingly distant relatives may evoke an eczematous dermatitis in the same individual. A classic example of this, so well worked out by Mayer (7), Baer (8), Laden (9), and others is the cross reactivity of the aromatic amine group of compounds which includes such commonly used agents as hair and fabric dyes, local anesthetics, sulfa drugs, and azo dyes, the latter being incorporated into many of our daily ingestants.

Space and practical considerations limit the discussion of antigen and antibody so that this is, necessarily, a very brief review of the antigen-antibody relationships in allergic dermatitis. However, it is impossible to deal intelligently with the allergic type of skin disease without some knowledge of its basic mechanisms.

CLINICAL TYPES

"Id" Reaction

Most common and probably best known of the "id" eruptions is the vesicular pruritic dermatitis of the hands which is secondary to an active focus of fungus disease of the feet (athlete's foot) (10). The mechanism for this distant eruption on the hands is not understood perfectly but probably the breakdown products of the fungi enter the circulation and reach the hands in this manner. Why the hands should be the most common and severe site for this eruption is unknown. Blood cultures have never revealed the presence of fungi during such an attack, and the fungi causing superficial skin lesions are practically impossible to culture from the blood. In addition, these fungi are not demonstrable in the "id" lesions of the hands. Therefore, it can be concluded that some breakdown product of the fungus, alone or

in combination with a protein, reaches the distant site through the circulation.

One type of cutaneous eruption due to penicillin is of interest in regard to "ids." This is the acute vesicular eruption in the groin, feet, and hands of people who were previous sufferers of superficial fungus infection. Penicillin, derived from a fungus, has antigenic properties apparently identical to the fungi of the superficial mycosis group and creates eczematous reactions at the sites of previous sensitization to fungi.

There are many other skin diseases based on similar mechanisms. Skin tuberculids are rather common and depend on an active tuberculous focus elsewhere, usually in the lungs or lymph nodes (11). Papulonecrotic lesions, indurated granuloma of the legs (erythema induratum), and papular erythematous lesions of the face (rosacea-like tuberculids) are all secondary to an active tuberculous focus elsewhere and never in themselves contain any demonstrable tubercle bacilli and always subside when the primary focus becomes inactive.

The concept of "id" eruption has been generalized to fit the observations in other bacterial and viral diseases where there is a known active infectious process with distant lesions which are commonly associated with the active lesion but never actually contain the organism and subside when the active focus subsides. Such eruptions are grouped as dermatomycids, bacterids, virids, syphilids, and so on.

Atopic Eczema

In its broadest sense the term atopic dermatitis includes dermatoses variously classified as nummular eczema, neurodermatitis, lichen vidal, infantile eczema, dyshidrosis, and a few others (12). An allergic basis for any of these disorders has been proved only in exceptional cases though there are many features of this disease group which provide suspicion for an allergic basis (13, 14). The histologic features of these diseases are intercellular edema and microscopic vesiculation along with dense lymphocytic infiltrates in the upper corium (15). This histologic appearance is the same as that seen in contact dermatitis with the exception that vesiculation is more prominent in allergic contact dermatitis.

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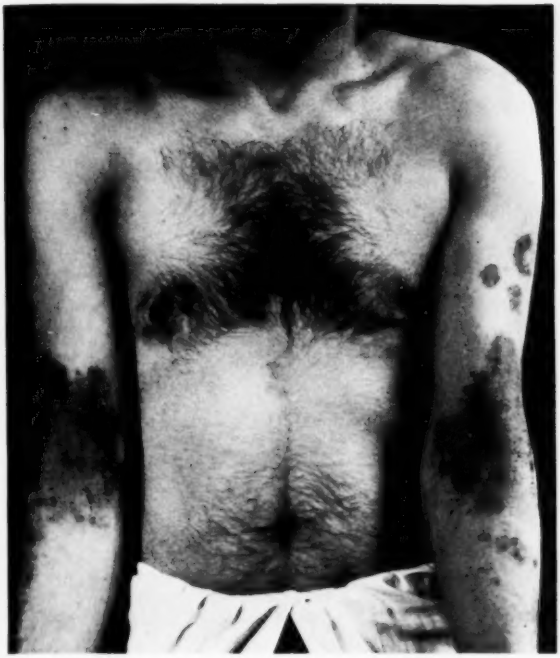

FIG. 1.—Neurodermatitis with characteristic flexural involvement.

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FIG. 2.—Infantile eczema with involvement of face, chest, and flexural areas.

FIG. 3 *(above)*.—Shows marked lichenification frequently present in neurodermatitis.

FIG. 4 *(below)*.—Flexural neurodermatitis with linear scratch marks.

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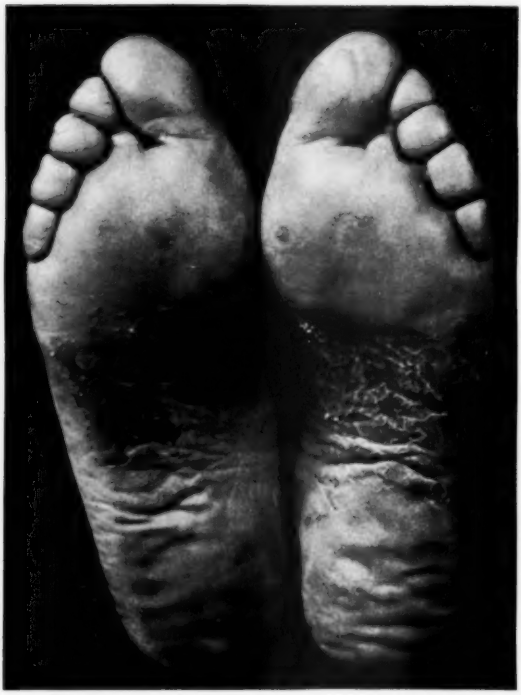

FIG. 5.—Dyshidrosis (neurodermatitis of the soles). This must be differentiated from a fungus infection, with which it is frequently confused.

FIG. 6.—Contact dermatitis resulting from contact with cement. Patient handled cement for six years before onset of dermatitis.

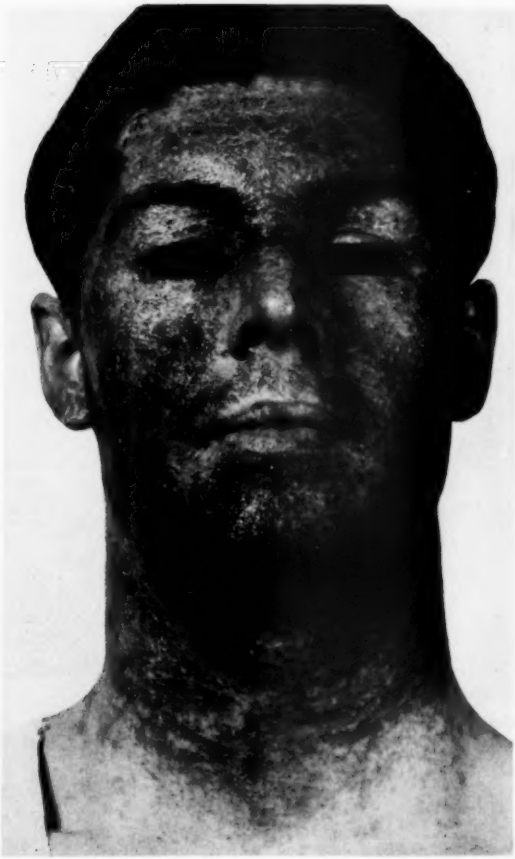

FIG. 7.—Contact dermatitis from ammoniated mercury ointment which he used for impetigo.

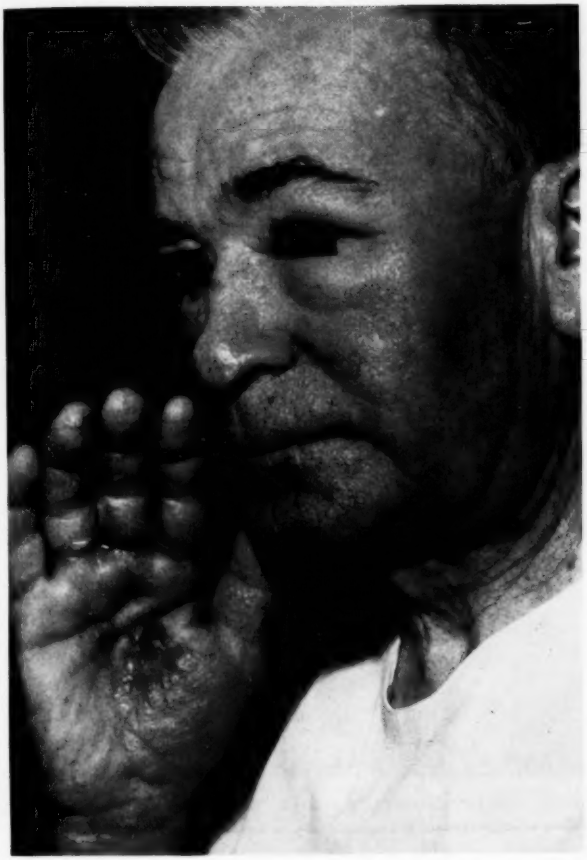

FIG. 8.—Contact dermatitis from phenol which he worked with on his job.

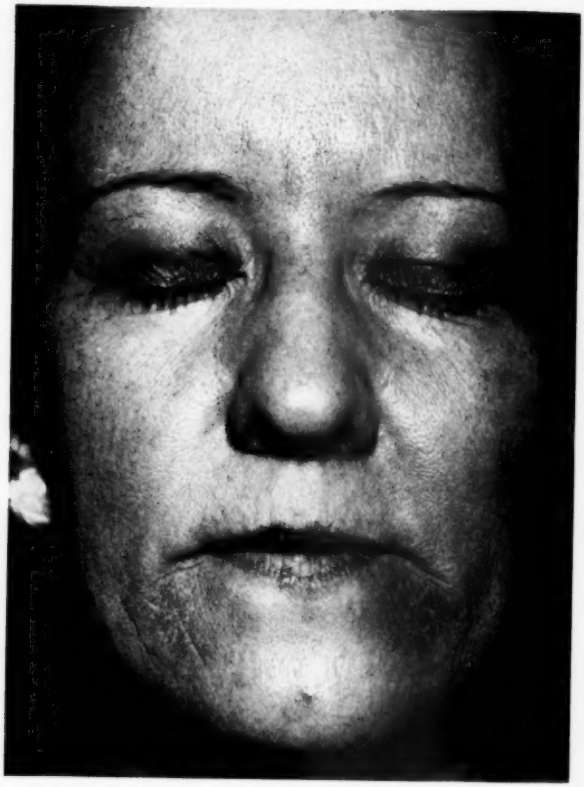

FIG. 9.—Contact dermatitis due to nail polish. Had previously been diagnosed as neurodermatitis.

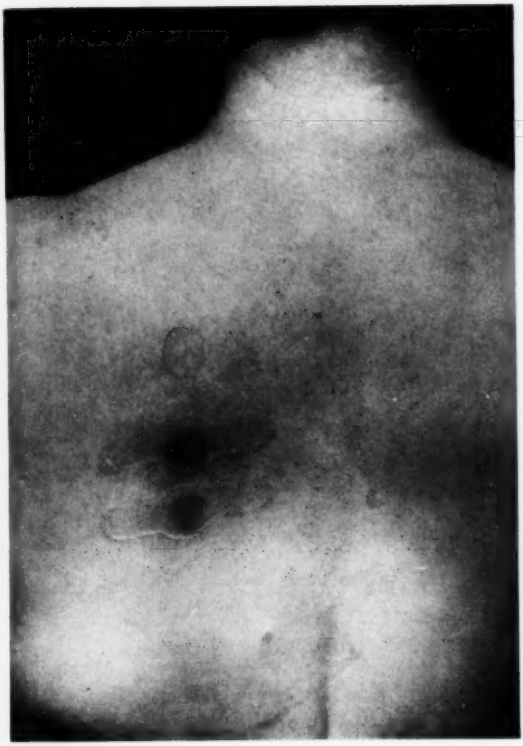

FIG. 10.—Positive patch tests to nail polish. Note erythema, edema, and very early vesiculation.

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FIG. 11.—Factitial urticaria (dermographism) showing the sharply elevated wheal in area of trauma and the surrounding flare.

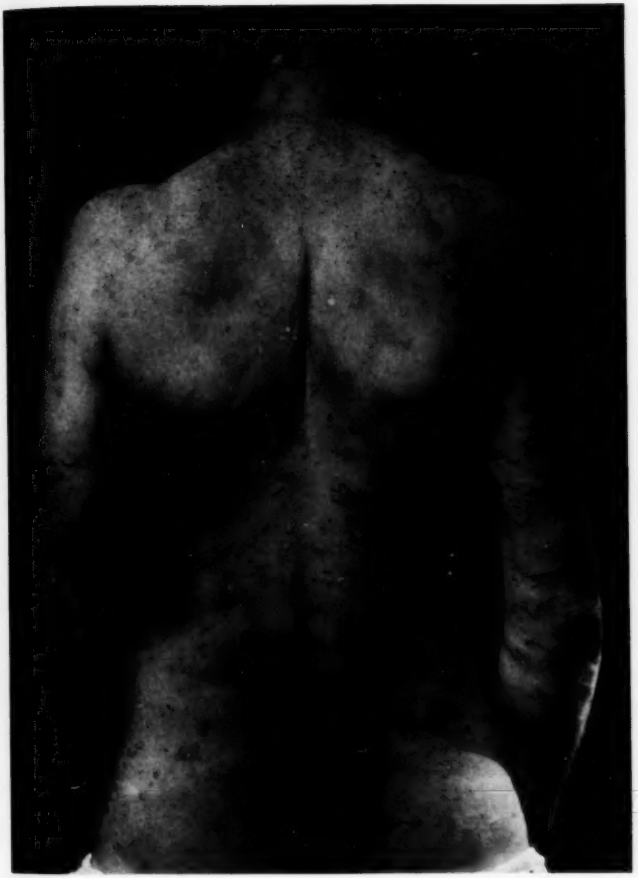

FIG. 12.—Urticaria. Lesions are sharply outlined, elevated, and of variable configuration.

FIG. 13.—Urticaria. Intradermal edema with pigskin appearance of lesions due to distention of follicles.

In the group of atopic dermatitis, there is a high personal and familial incidence of asthma, hay fever, and urticaria, which are also diseases with a strong background of allergy. Circulating antibodies to a number of substances can be demonstrated in atopic eczema and rather characteristically these patients display urticarial reactions to a large variety of substances commonly used in scratch and intradermal testing. These positive reactions suggest an allergic basis, but again the causative allergen, if there is any, is rarely identified, and the practical approach to managing this disease group is, if anything, obstructed by trying to manage it as if it were based on mechanisms of allergy.

The typical lesions of atopic eczema (Figs. 1 to 5) are characterized by lichenification, erythema, excoriations, and scaling. The common areas of involvement are the flexor surfaces of the elbows and knees, the nape of the neck, the face, axillae, and inguinal areas. It is almost without exception a severely pruritic disease, which frequently awakens the patient at night. It has a natural tendency to spontaneous improvement in summer and exacerbation in winter. Most cases benefit by a change in environment, especially if it be to warmer geographic areas. It is chronic and recurrent. Many sufferers develop the disease shortly after birth and may never be free of it even into late adult life. In others, the lesions may first appear during childhood or adolescence or may even appear for the first time late in life. It is difficult to make a prognosis in any one case but, in general, the earlier in life it appears and the greater the extent of the disease, the more severe and prolonged it is likely to be.

There is no doubt that emotional upsets, various tensions, and lack of rest are all detrimental in this disease, and that superficial psychotherapy is of limited value. There is also no doubt that soap and water, low absolute humidity, and scratching are very harmful. But these are aggravating and not etiologic factors.

TREATMENT.—Both local and systemic therapy are of value in treating this disease group (16). In the exudative, acute stages of the disease, open wet dressings (see CONTACT DERMATITIS) and protective ointments, preferably with bandaging, are the methods of choice. Hydrocortisone or prednisolone ointments are also of help in the acute and subacute stages. The steroids, locally, are an aid to treatment but are rarely enough by themselves to control the disease (17). In the less acute phase, ichthyol 2–5% or

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special tar derivatives are used (see formulas below) with linen bandages which are changed along with the ointment twice a day.

1. Ichthyol	2.4–6
Zinc oxide	20
Yellow petroleum q.s. ad	120
2. Tar distillate	2.4–6
Zinc oxide ointment } aa q.s. ad	120
Yellow petrolatum }	

Systemic treatment is aimed primarily at sedating the patient (phenobarbital, bromides, the so-called tranquilizing drugs), decreasing sweating (banthine,® pro-banthine,® or atropine), and controlling secondary infection. In exceptional instances where the disease is unusually severe and persistent in the face of all other therapy or there is a serious threat of suicide because of the disease (and this is not uncommon), corticotropin, hydrocortisone, or prednisone, systemically, will frequently give dramatic initial improvement. However, it is best to avoid these drugs if possible in the management of atopic dermatitis.

Contact Dermatitis

Contact dermatitis is also known by the terms allergic eczematous dermatitis and dermatitis venenata. It is probably the most common type of allergic dermatitis, having only one close competitor in this regard—dermatitis medicamentosa. It is frequently misdiagnosed and presents a high potential reward to both physician and patient when properly diagnosed. The offending agent can be shown by patch tests to cause a dermatitis on normal skin; the patient then avoids this agent in his job, recreation, or wherever in his environment it might be, and he is cured. There are too few diseases where this type of satisfaction can be obtained.

The main reason contact dermatitis so frequently is misdiagnosed is that the examiner does not think of the possibility or if he thinks of it, he does not ask the right questions. The more experience one has with contact dermatitis the more intuitive one becomes. The enlightened interviewer who suspects a contact dermatitis will make Sherlock Holmes appear a naive schoolboy, and the stereotyped nagging housewife seem gentle by comparison. Consider the questions and detective work that must have been necessary to arrive at the following diagnoses:

1. Contact dermatitis of the penis from spermacidal jelly used by the patient's wife's surreptitious lover.
2. Contact dermatitis of the face, neck, lower arms, and lower legs caused by an insecticide spray from a distant neighbor. (It always started in the spring and flared up during "hot spells" when the wind was from the west, where the distant neighbor was located.)
3. Contact dermatitis of a young housewife's eyelids from her mother-in-law's perfume. Her difficulty had been previously diagnosed as neurodermatitis precipitated by the visits of her mother-in-law.
4. Poison ivy dermatitis on the hands of an invalid who had been confined to the house for 2 years. The family dog picked up the allergen on his fur and brought it home to his master.

There are, no doubt, many patients with persistent and recurrent dermatitis of a contact nature who have been thoroughly studied by allergists and dermatologists in addition to other physicians and are still unwittingly contacting an agent responsible for their dermatitis. However, diligent pursuit of all possible sources can usually reveal the causative agent.

The clinical picture of a contact dermatitis (Figs. 6 to 10) characteristically consists of pruritus, erythema, edema, vesiculation, and exudation in the acute type of reaction, but may show erythema, scaling, and lichenification in areas of chronic, repeated exposure. The one clinical sign most suggestive of contact dermatitis is vesiculation and it is present most of the time. Frequently the area of involvement will suggest the offending agent (see Table 2).

TABLE 2

Area	Possible Causes
Scalp and forehead	Dyes, straighteners, oils, perfumes, metallic agents for the hair, hatbands
Eyelids	Nail polish, cosmetics, plants, sprays, dyes
Face	Lotions and shaving creams, cosmetics, sprays, flowers, local medicaments
Neck	Clothing, perfume, costume jewelry
Hands	Any of literally hundreds of things contacted each day
Trunk	Clothing, local medicaments, belts, metallic pieces on clothes, articles carried in pockets
Penis, perineum and perianal	Condoms, contraceptive jellies, clothing, toilet paper, medicaments, elastic supporter
Feet	Shoes, medicaments

The occupation (18, 19) of the individual may immediately suggest one or more possible contact agents responsible for the eruption (see Table 3).

TABLE 3

Occupation	Common Sensitizing Agent
Aircraft manufacturing	Chromates, "dopes," resins
Artist	Solvents, oils, glazes
Carpet and rug industry	Dyes, bleaches, benzene
Dentist	Procaine, mercury, plastic
Explosives manufacturing	Tetryl, TNT, picrates, mercury
Farmer	Insecticides, fertilizers, oils
Florist	Sprays, flowers
Lithographer	Hydroquinone, chromate
Machinist	Cutting oils, metals
Nurse	Streptomycin, penicillin, medicaments
Undertaker	Formalin, mercury

Because of its high incidence as well as conformity to other types of contact dermatitis, a few special words about poison ivy dermatitis seem indicated. There is a definite variation in degree of sensitivity among those who are allergic to poison ivy. Some will break out with incapacitating bullous eruptions if they literally come near the plant, especially when it is burning or being traumatized. Others may get only slight erythema after direct exposure to the crushed leaf. Spontaneous loss of sensitivity to poison ivy is practically unheard of. Desensitization by injections of poison ivy extract is a claim frequently made and rarely proved. "Spreading" of the dermatitis by blister fluid does not occur, a fact established over 150 years ago and very entertainingly reviewed by Rostenberg (20). One may become allergic to poison ivy at any age after having been previously "immune" even in the face of multiple previous exposures. The greater the number of exposures, and the greater the concentration of each exposure, the more likely is one to become sensitized (3). There is no way to predict who will and who will not become sensitized.

The above facts about poison ivy contact dermatitis hold equally well for contact dermatitis from almost any agent.

Observations of contact dermatitis among industrial workers has led to some interesting conclusions. People with dark skin are less likely to develop contact dermatitis than people with light skin. Whether this is due to the concentration of melanin pigment alone is unknown, but unlikely. Two fairly well substantiated observations are that (1) an individual sensitive to a particular chemical may, after further regular contact with this chemical, develop some resistance (hardening) to it and (2) if

an individual becomes allergic to any one chemical, he may then become allergic to many chemicals which are unrelated to one another (polyvalent sensitivity) (10).

The patch test has been of immense value in investigating individuals suspected of contact dermatitis. The agent in question is applied to normal skin, covered with a linen patch which is then covered by an occlusive material, usually cellophane, and then taped in place. Special patches for this purpose are available commercially. The suspected allergen is kept in place for 48 hours after which it is removed. Reactions range from 1–4 plus on a scale of (1) erythema, (2) erythema and edema, (3) erythema, edema, and tiny vesicles, and (4) large blisters and occasional necrosis. A control is always put on with the others and should be completely negative. It is not uncommon to get all sorts of reactions to the tape but it is rare that the occlusive cellophane and linen patch will, by themselves, give any reaction. One can test for numerous suspected agents at one time. The author has applied up to 50 patch tests at one time with this method.

Care should be taken to try to duplicate the conditions under which the patient was actually exposed to the agent. Was it in a dry form? Was it in solution? What was the solvent? In what concentration was the agent? Was the patient active or sedentary during natural exposure? Was he perspiring? Was it humid or dry? All conditions should be duplicated as nearly as possible.

Because the sensitization of contact dermatitis is almost always instantaneously universal over the entire cutaneous surface, any area is potentially capable of eliciting the dermatitis on exposure to offending agent. A possible exception is mucous membrane which may be sensitized independently from the cutaneous surface. In such a case the patch test should be on mucous membrane (21).

Care should also be taken in patch testing while the individual has a dermatitis. There is a definite possibility of getting a severe flare-up of the existing lesions along with the positive patch test.

The proper concentrations of various chemicals and the diluent to be used for patch testing have been established for numerous agents which can cause sensitization. A sizable list has been compiled by Sulzberger (22).

TREATMENT.—Treatment of contact dermatitis is, of course, satisfactory only if the offending agent is avoided. The acute, ex-

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udative reactions such as that seen in poison ivy eruptions are best treated with wet dressings and bandaging with a bland covering such as zinc oxide ointment.

Wet dressings should be applied so that there is continuous evaporation and cooling. No occlusive covering should be used. Potassium permanganate (concentration of 1/8000 in tap water) is frequently used. It is imperative that the solid $KMnO_4$ be completely dissolved before use or particles of $KMnO_4$ which are not completely dissolved will cause primary necrosis in areas of contact with the skin. Other compounds such as boric acid or aluminum subacetate may also be used. The most important action of wet dressings is to allow a continuous and mild cooling effect on the inflamed areas which results in vasoconstriction and reduction of the inflammatory reaction.

Protective ointments should be bland and should not contain local anesthetics, antihistaminics (23), or other unnecessary medicaments which frequently act as potent sensitizers and are rarely of significant help to the patient either objectively or subjectively. After the ointment is applied thickly it should be covered with soft linen. The ointment should be removed gently with mineral oil and reapplied twice a day.

Local application of a bland lotion will give symptomatic and objective relief in many cases. For most cases a bland ointment with bandaging is superior to lotions. However, if the eruption is severely exudative in nature or the environmental temperature is excessively high, lotions may be more advantageous. Simple calamine lotion is adequate, though it is difficult to obtain a simple calamine lotion anymore that does not have such potent sensitizers as antihistaminics or nupercaine or benzocaine, etc., added to it. The formula for a good basic lotion is:

Zinc oxide	45
Talc	45
Glycerin	20
Olive oil	20
Water q.s. ad	200

Local application of hydocortisone diminishes the inflammatory response to a mild degree and perhaps shortens the course of the disease, but secondary infection is more likely to take place with its use and the expense, especially if large areas are involved, is considerable. Oral use of hydrocortisone, cortisone, or prednisone definitely decreases the inflammatory response and gives ob-

jective as well as subjective improvement, but again the side reactions resulting from the use of these drugs may result in a disease worse than the original contact dermatitis. One should be cautious and selective in the use of steroids for contact dermatitis.

Attempts at desensitization are almost uniformly unsuccessful. Desensitization therapy during an active phase of the disease is irrational and attempts to do so have resulted in disastrous aggravations.

Urticaria

The urticarial reaction (Figs. 11 to 13) may be initiated by a wide variety of factors (trauma, heat, cold, light, penicillin, protein, and so on) but the ultimate chemical substance responsible for the classical triple response (erythema, edema, flare) is histamine. More recent work has indicated a number of compounds which have the ability of releasing histamine in skin and thereby provoking an urticarial response.

It is advantageous, clinically, to divide urticaria into acute and chronic types. In the acute form, an etiologic agent can usually be found, whereas in the chronic type the etiologic agent is rarely identified. When urticaria is due to a known agent such as penicillin, horse serum, aspirin, fish, seafood, cucumbers, sting of a jelly fish, or barb from a nettle, there is, of course, little trouble in establishing the etiology and avoiding the causative agent in the future. Most provoking of all the urticarial eruptions, however, is the type that goes on and on for months and years and for which an etiologic agent can seldom be demonstrated. These usually end up being classed as psychogenic urticaria and it is difficult to tell which came first, the urticaria or the nervousness.

It is in chronic urticaria in which no etiology can be established that extensive skin tests are usually performed. It is generally agreed that skin tests are almost valueless in this disease. Positive reactions are frequently seen, but desensitization and avoidance of the agent giving the positive reaction do not influence the course of the disease. It has also been shown that true allergens may give a negative scratch test but a positive passive transfer reaction. This is more understandable when one considers that the active allergens—of a food for instance—may only be released after alterations have taken place in the gastrointestinal tract or after absorption through the intestinal wall. Similarly, a medicament functioning as an allergen usually needs to

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be altered within the body before its true antigenic nature becomes apparent. Conversely, a medicament or food might contain a histamine liberator or antigen in its natural form and give rise to a positive skin test. However, it is most likely that this agent will be completely modified in the body so that it will not be a histamine liberator or act as an antigen when it finally reaches the skin in its altered form. Such a situation would, of course, give a false positive scratch test. In the practical management of allergic dermatitis, scratch tests are of limited value.

Many individuals with chronic urticaria have a personal or family history of the eczema-asthma-hay fever complex. Also, as in eczematous patients, they frequently have circulating antibodies and show urticarial reactions to a great variety of substances injected or scratched into the skin.

A remarkable group of urticarial reactions is that caused by physical agents (24). Ultraviolet light, trauma, heat, or cold may produce an urticarial reaction at the site of action or even provoke a general urticarial eruption following local exposure. Actual circulating antibodies can be shown and positive passive transfer tests have been reported for all these physical urticarias. Some people develop urticaria after exposure to ultraviolet light in the 2900 Å range and others only to light of wavelength near 4000Å. The urticarial reaction following mild trauma and commonly known as dermographism is quite well known (Fig. 11). The nature of the actual antigen is not known but there is good evidence to suggest an antigen-antibody mechanism for all the physical urticarias.

TREATMENT.—*Antihistaminics:* As these drugs have definite antagonistic action to histamine, they are the logical choice for treating urticarial eruptions, probably all of which are ultimately caused by histamine liberation. The antihistaminic preparations give some relief to practically all patients suffering from urticaria, but it is unusual that complete control of the urticarial eruption is achieved even with rather high doses of the drug. Frequently, two or three different antihistaminics can be combined, giving a standard dosage of each, and not precipitate the toxic reactions that might arise from an equivalent dose of any one of the two or three drugs used. Actual sensitization to the various antihistaminics is not uncommon and must be watched for, especially because the cutaneous reaction to these drugs may be confused with the urticarial eruption being treated.

Local application of antihistaminics is useless for they do not penetrate the normal epidermal barrier present in urticaria.

Sedation: Though sedatives have no specific action on the urticarial eruption, they are frequently of value because of the nervousness and sleeping difficulties common in people with this severely pruritic disease.

ACTH and steroids: These drugs have been of great value in giving symptomatic and objective relief in both acute and chronic urticaria. They have no effect in shortening the disease and seem not to influence the basic disease process in any way other than suppressing it during its preordained course.

It is curious that despite large doses of ACTH, cortisone, hydrocortisone, or prednisolone, given intravenously, intramuscularly, or orally, there is always a lag of 12 to 36 hours between its administration and subjective or objective relief. Local application of steroids is of no value.

Epinephrine: For immediate subjective relief there is no drug superior to epinephrine. A sufficient dose is usually 0.2–0.4 cc. of a 1/1000 solution given intramuscularly. Relief is temporary, lasting not longer than one hour. Epinephrine in oil for a more sustained effect is rarely satisfactory in that usually there is little effect because of the slow absorption. Or, in some individuals, the absorption may be quite rapid and give not only subjective relief but severe side reactions because of the higher doses used, as a rule, when oil preparations are given.

Local applications: At best, local applications give minimal relief. However, lotions with phenol or menthol or both are frequently used. Local applications containing anesthetics of the procaine series or antihistaminics should be avoided.

Dermatitis Medicamentosa

Any eruption of the cutaneous surface and mucous membranes which results from the introduction into the body of a medicament may be termed dermatitis medicamentosa. Some of the most common examples are (1) urticaria resulting from penicillin and horse serum, (2) morbilliform eruptions from barbiturates and sulfonamides, (3) fixed drug eruptions from phenolphthalein in laxatives, (4) acneform eruptions from iodides, bromides, ACTH, and steroids, and (5) eczematous dermatitis from quinidine, arsenicals, and penicillin.

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There is hardly a drug in existence which has not caused a dermatitis in someone. Most drug eruptions are probably "allergic" in nature but some, such as the acneform eruptions, may not be dependent on a basic allergic mechanism.

When applied locally the sensitizing potency of such drugs as penicillin, sulfa drugs, local anesthetics such as novocaine, benzocaine, and nupercaine, and antihistaminics is so high and the resulting dermatitis so severe and prolonged that they should *never* be used in topical application. The use of these compounds, topically, cannot be justified. There are other agents which accomplish the same effect with far less danger of sensitization. Such antibiotics as polysporin,® bacitracin and neomycin should be used instead of *any* of the antibiotics which are widely used for systemic therapy, not only because of the reduced danger of sensitization but also because an individual might be sensitized to a valuable antibiotic which he might need desperately at a later date. We still see streptomycin put into ointments for such things as acne, impetigo, boils, or even dry skin. This is an unpardonable practice.

It is well to remember the various routes by which drugs may be introduced to the body as it is of great help in questioning the patient about possible sources of the dermatitis medicamentosa. Vaccines, antitoxins, insulin, ACTH, diuretics, and other compounds given by injection, medicaments in douches, rectal suppositories, linguettes, nasal and urethral irrigations, and eye drops may be at fault. Toxic substances may be inhaled and enter through the pulmonary system. These are rather obvious, perhaps, but frequently overlooked by the historian who attempts to locate the offending agent.

Each new "wonder drug" leaves in its wake a certain percentage of cutaneous eruptions, many of them severe and occasionally fatal. The author recently saw a patient almost die with a severe bullous erythema multiforme precipitated by an "anti-nausea" antihistaminic. She had taken chlorpromazine 2 months earlier, but it was stopped after jaundice appeared. One month later the "anti-nausea" antihistaminic was given. This antihistaminic had the same basic chemical structure as chlorpromazine and the patient developed a nearly fatal sensitization reaction. Once one becomes allergic to one drug, one is likely to be allergic to all drugs in the same chemical group. Thus, once allergic to one antihistaminic, watch out for all antihistaminics. The same

holds true for all the sulfa drugs, all the barbiturates, all the local anesthetics, and many other drug "groups." Table 4 lists many common drugs and the usual types of cutaneous reactions.

TABLE 4

Drug	Reaction Types
ACTH (corticotropin)	Urticaria
Amidopyrine	Fixed eruption; urticaria
Anesthetic (procaine series)	Erythema; urticaria
Antibiotics (penicillin, aureomycin)	Eczematous reaction; urticaria
Antipyrine	Fixed eruption; erythema; purpura
Antihistaminics	Urticaria; morbilliform erythema; erythema multiforme
Arsenicals:	
a) Inorganic (Fowler's solution)	Keratoses; pigmentation
b) Organic (Mapharsen, etc.)	Vesicular, urticaria; purpura; exfoliative dermatitis
Barbiturates	Morbilliform erythema; urticaria
Bromides	Acneform dermatitis; vegetative dermatitis
Digitalis	Morbilliform erythema
Ephedrine	Eczematous dermatitis
Ergot	Gangrene of extremities
Gold	Exfoliative dermatitis; morbilliform erythema; chrysiasis
Insulin	Urticaria; local fat necrosis
Iodides	Acneform dermatitis; bullae; vegetative dermatitis
Phenolphthalein	Fixed eruption
Quinidine	Eczematous dermatitis; morbilliform erythema
Salicylates	Erythema multiform; erythema nodosum; urticaria
Serum	Urticaria; anaphylactoid response, fever, lymphadenopathy; edema
Silver	Argyria
Sulfonamides	Morbilliform erythema; erythema nodosum; eczematous, bullous, exfoliative dermatitis

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